LOW "GRADIENT", LOW FLOW AORTIC STENOSIS

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Aortic stenosis is thought to have a long, asymptomatic latent phase during which the risk of sudden death is low. In fact symptoms can be revealed by treadmill exercise in a large proportion of apparently asymptomatic patients.[1] Patients may limit exercise to avoid symptoms or may fail to recognise the presence of exertional breathlessness or ascribe it to old age or some other condition. Such patients may then present in heart failure with relatively advanced disease when the left ventricle decompensates.[2] Even in the presence of overt symptoms, physicians may fail to make the diagnosis[3] often in the mistaken belief that severe aortic stenosis cannot coexist with systemic hypertension.[4] Sometimes heart failure is precipitated in truly asymptomatic aortic stenosis by myocardial infarction, sepsis or another stress like non-cardiac surgery. For these reasons, the initial presentation for about 5% of patients having surgery is with heart failure[5] rather than exertional chest pain or breathlessness. The four year survival of patients with a low ejection fraction and mean transaortic pressure difference < 30 mm Hg is only 35% compared with a survival of 60% if the mean pressure difference is > 30 mm Hg.[6] Management decisions centre on confirming the grade of aortic stenosis and determining whether the left ventricle is likely to recover after surgery.

WHAT IS LOW "GRADIENT", LOW FLOW AORTIC STENOSIS?

Criteria for grading aortic stenosis with normal left ventricular function are given in table 1. However, the transaortic velocity and derived pressure difference are flow-dependent while effective orifice area by the continuity equation is relatively flow-independent (fig 1). Heart failure causing low systolic flow can therefore lead to a patient with severe aortic stenosis having an apparently moderate transaortic pressure difference associated with a low effective orifice area. The hope in this clinical situation is that aortic valve replacement will relieve afterload and allow the left ventricular ejection fraction to increase towards normal.[2] However, recovery may be incomplete[7 8] if there is severe fibrosis secondary to aortic stenosis. The echocardiographic findings may also be similar in a patient with moderate aortic stenosis in the presence of a myocardial infarct or other cause of left ventricular dysfunction. The effective orifice area is then low because the left ventricle does not generate sufficient energy to overcome the inertia required to open the aortic valve to its maximum possible extent. In this situation, aortic valve replacement may not lead to an improvement in left ventricular ejection fraction.

"Low gradient, low flow aortic stenosis" has been defined in the literature by a variety of different cut points. The most inclusive is an effective orifice area < 1.0 cm^2,[9–11] LV ejection fraction < 40%, and mean pressure difference < 30 mm Hg.[5 11 12] In such patients, the first step must be to recognise that the aortic stenosis could be severe.

RECOGNISING THE PROBLEM

Thinking of echocardiography

The elucidation of clinical signs in aortic stenosis may be unreliable.[4] The carotid upstroke is reported as normal in half of patients with severe aortic stenosis[13] and one study found a narrow pulse pressure (< 35 mm Hg) in only 7% having aortic valve surgery.[14] As flow falls in critical aortic stenosis, the murmur may become imperceptible. Every patient with a clinical diagnosis of heart failure should have echocardiography, particularly when the aetiology is not known or if there is even an apparently trivial murmur. To detect aortic stenosis with a view to judicious timing of surgery before the onset of heart failure, every patient with anything more than a short, soft ejection systolic murmur and a well-heard second heart sound should have an echocardiogram.

Thinking of severe aortic stenosis

Calculation of effective orifice area (fig 1) is essential whenever a thickened, immobile aortic valve is associated with a reduced LV ejection fraction. A useful prompt to consider severe aortic stenosis is a continuous wave signal with a "gothic arch" waveform shape[15] (fig 2). With primary

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Table 1 Grading aortic stenosis with normal left ventricular systolic function

	Mild	Moderate	Severe
Peak velocity (m/s)	<3.0	3.0–4.0	>4.0
Mean pressure difference (mm Hg)	<15	15–40	>40
Effective orifice area (cm^2)	>1.4	1.0–1.4	<1.0

left ventricular dysfunction, the left ventricular ejection time is short.[16] With severe aortic stenosis, the left ventricular ejection time and the time to peak velocity both lengthen.[17] This makes the waveform shape relatively broad and symmetrical (fig 2). This shape is maintained even when the peak velocity falls as left ventricular dysfunction develops.[15] By contrast, more moderate aortic stenosis is associated with a dagger-shaped signal (fig 2). The shape can reasonably be appreciated by eye. However, a simple semiquantitative description of the shape is provided by the ratio of the peak to the mean pressure difference. If this is < 1.5, the aortic stenosis is almost invariably severe. If the ratio is < 1.7, it is likely that the aortic stenosis is severe.[15] Imaging the aortic valve using either transoesophageal echocardiography or magnetic resonance is not appropriate. Although clearer images of the valve orifice can be obtained, aortic stenosis is graded by the effective or hydrodynamic orifice area rather than the anatomical orifice area.

Echocardiographers should also assess right ventricular function and estimate pulmonary pressures in patients with severe aortic stenosis. Pulmonary hypertension is common[18] and is associated with a particularly high perioperative risk.[19]

Flow correction

Calculating the effective orifice area using the continuity equation is the standard method of obtaining a relatively flow independent measure of valve function. However, flow correction by calculating resistance may sometimes be more representative. Although pressure drop is usually related to the square of flow via the Gorlin formula for experiments in vitro, this relationship looks linear over a narrow change of flow in the physiological range.[20] Resistance assumes a linear relationship between flow and pressure drop and is the simple ratio of mean pressure difference over flow calculated as: Resistance (dynes.s.cm^{-5}) = [1.333 × mean pressure difference (mm Hg) × systolic ejection time (ms)]/stroke volume (ml).

Resistance might be more sensitive than effective orifice area for detecting severe aortic stenosis because there is a curvilinear relationship between the two quantities which means that resistance changes more at the border between moderate and severe stenosis. Furthermore, although both are calculated using similar waveforms, the calculation required for resistance incorporates the ejection time, which, as discussed above, independently reflects the grade of aortic stenosis. Furthermore, ejection time and mean pressure drop are relatively easily measured and accurate while errors are possible in the positioning of the pulsed Doppler sample within the subaortic region and in the measurement of left ventricular outflow tract diameter.

The potential benefit of resistance was shown by Cannon *et al*.[21] These authors studied patients with low flow aortic stenosis and effective orifice area < 0.6 cm^2. These were divided into those with genuinely critical stenosis confirmed

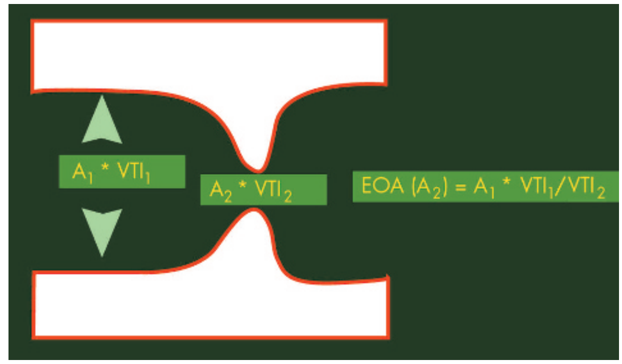

Figure 1 The continuity equation. The continuity equation is based on the law of conservation of mass. In a closed system, the stroke volume below the valve must be the same as the stroke volume through the valve. The stroke volume below the valve is calculated from the product of the cross-sectional area of the LV outflow tract (A_1) and the area of the pulsed Doppler waveform (VTI_1). The effective orifice area of the valve (A_2) can be calculated by dividing this stroke volume by the area of the continuous waveform (VTI_2). Peak velocity has sometimes been used as an approximation for the area of the waveform. The ratio of the subaortic and transaortic peak velocities will only be similar to the ratio of the areas if the pulsed and continuous wave signals have the same shape.

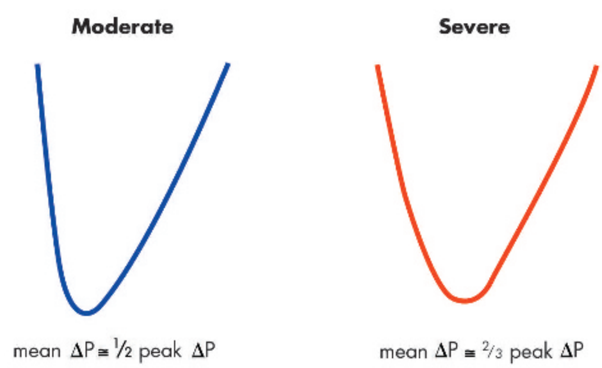

Figure 2 Waveform shape. The continuous wave signal in patients with moderate aortic stenosis has a relatively fast upstroke and the mean gradient is approximately half the peak. In patients with severe stenosis, the ejection time and the time to peak velocity are both prolonged. The mean gradient is approximately two thirds the peak. Current evidence[15] shows that the aortic stenosis is always severe if the peak divided by the mean pressure difference is < 1.5 and dobutamine stress should be performed to clarify the diagnosis if the ratio is < 1.7.

Table 2 Measures based on systolic ejection time

Relative ejection time (s)

- Expected ejection time[17] (in seconds) is 0.002 × stroke volume (in ml) + 0.106. If the observed ejection time is more than 0.7 s longer than expected from the left ventricular ejection fraction, it is likely that the aortic stenosis is severe

The Tei index

- This is calculated as (IVRT + ICT + EJT)/EJT where IVRT and ICT are isovolumic relaxation and contraction times and EJT is ejection time. A Tei index >0.42 has been reported to differentiate almost all patients with severe aortic stenosis and left ventricular dysfunction from control subjects or patients with aortic stenosis and preserved left ventricles[24]

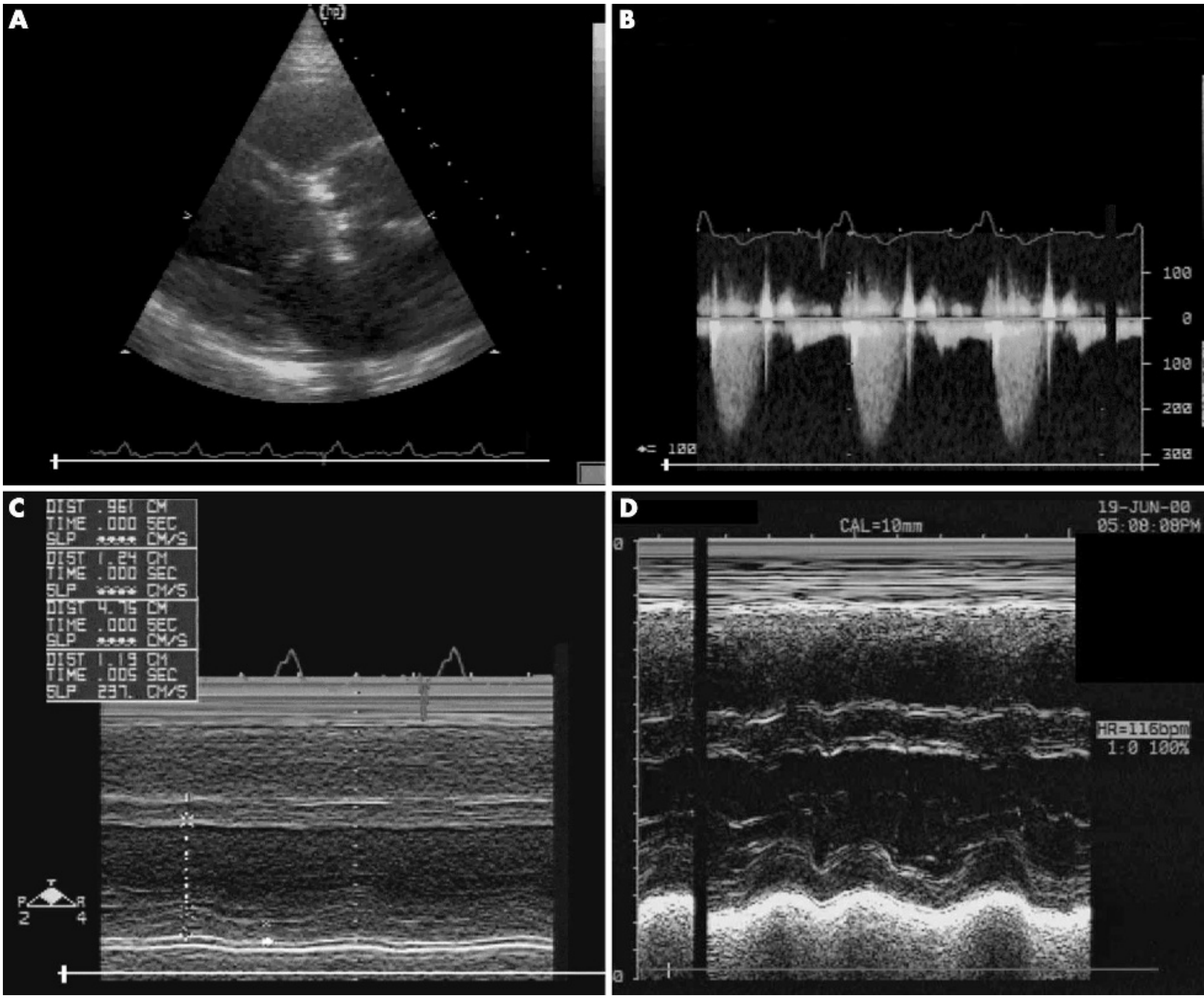

Figure 3 Dobutamine stress in low gradient, low ejection fraction aortic stenosis. This patient presented in heart failure. The left ventricle was dilated and globally hypokinetic as illustrated in this parasternal long axis late systolic frame (panel A). The left ventricular ejection fraction was 15% and the peak transaortic velocity was 3.0 m/s (panel B), despite a dobutamine infusion at a dose of 5 μg/kg/min. Increasing the dose to 10 μg/kg/min increased the systolic velocity integral by 33% from 4.8 cm to 6.4 cm. The patient recovered well and now has normal exercise tolerance although he is in atrial fibrillation. The M mode before surgery during dobutamine infusion is shown in panel C and after surgery in panel D.

by surgical inspection and those that were less severe. These two groups were reliably differentiated by a resistance over 200 dynes.s.cm^{-5}. However, a number of authors have found that resistance either increases, decreases or stays constant with flow.[22] This is probably because mean orifice area changes[23] either as a result of an increase in maximum geometric orifice area or because the valve opens more quickly, or both. In practice resistance is not usually more reliable than effective orifice area. Similarly methods based on time intervals are not routinely used[16 17 24] (table 2). The definitive investigation for patients with low gradient, low flow aortic stenosis is dobutamine stress echocardiography.

Dobutamine stress

Dobutamine both aids the grading of aortic stenosis and, more importantly, tests for left ventricular contractile reserve. Doses between 5–10 μg/kg/min and sometimes 20 μg/kg/min are given in increments of 5 μg/kg/min approximately every five minutes.[10 23] There is a risk of arrhythmia so there must be medical supervision; high doses of dobutamine should be avoided and the infusion can be stopped as soon as a positive result is obtained.

In general, severe aortic stenosis is associated with a relatively large rise in mean pressure difference and a relatively small rise in orifice area. By contrast, moderate stenosis is associated with a small rise in mean pressure difference and a larger rise in effective orifice area. However, there is no rigid division into fixed and relative aortic stenosis as was suggested by a small preliminary study.[25] In patients with normal left ventricular function, the effective orifice area increases by about 25% in all grades of aortic stenosis although the absolute increase is less in severe stenosis than in moderate or mild stenosis.[23] Severe stenosis is suggested[11] by a failure of the effective orifice area to increase above 1.2 cm^2 or by a compliance of $<$ 0.2 cm^2/100 ml/s as calculated from the plot of effective orifice area and flow.[23] A simpler practical guide is a rise in the mean pressure difference above 30 mm Hg at any time during dobutamine infusion.[11]

In fact, surgical results in patients with low flow aortic stenosis depend less on the grade of stenosis or even on the resting LV ejection fraction than on the ability of the left ventricle to recover.[10 13 26] Therefore, the most important observation during dobutamine infusion is whether the ventricle improves. If the systolic velocity integral reliably increases by more than 20%, the surgical mortality is relatively lower and the mid term outlook relatively better than if there is no such increase (fig 3). The early surgical mortality is 5–7% in patients with flow reserve and 32–33% in those without flow reserve.[11 26] Survival at five years was 88% after surgery in the presence of flow reserve, but between 10–25% if there was no reserve.[10]

EFFECT OF ECHOCARDIOGRAPHY ON CLINICAL MANAGEMENT

A patient with a low ejection fraction but mean transaortic pressure difference above 30 mm Hg or peak transaortic velocity > 3.5 m/s on the standard echocardiogram does not have a poor left ventricle.[2] The ventricle is demonstrating a normal response to high afterload and the surgery can be undertaken with higher than average risk, but with the likelihood of good long term survival. This patient does not need a stress echocardiogram.

However, dobutamine stress echocardiography is always needed for patients with a mean transaortic pressure difference below 30 mm Hg at rest. Surgery can be undertaken at acceptable risk if the systolic velocity integral rises by > 20% during dobutamine infusion and if the effective orifice area by the continuity equation remains < 1.2 cm^2. Pulmonary hypertension increases the operative risk and is associated with a poorer long term result,[19] but does not on its own contraindicate surgery.

If the patient has severe aortic stenosis, but the stroke volume does not increase by more than 20% during dobutamine infusion, the surgical risk is high and long term outcome poor.[10] However, the outlook without surgery is dismal so that in selected patients without significant co-morbidity it may be reasonable to proceed with surgery after careful discussion with the patient and family.

In patients in whom echocardiography has shown relatively moderate aortic stenosis with or without flow reserve, the literature suggests that surgery should not be performed. However, in individual cases the decision to withhold surgery remains difficult. If the effective orifice area is well above 1.2 cm^2 with dobutamine and there is an obvious alternative cause for the left ventricular dysfunction, such as coronary disease with a fixed scar, it is reasonable not to operate. If, however, the effective orifice area is around 1.2 cm^2, the left ventricular dysfunction is global and there is no obvious alternative cause, surgery should still be considered. Anecdotally, patients with relatively moderate stenosis can develop significant left ventricular impairment and both require and do well with aortic valve replacement.

CONCLUSION

Aortic stenosis with low gradient and low left ventricular ejection fraction can be caused by critical aortic stenosis causing left ventricular impairment or by more moderate aortic stenosis coexisting with another cause of left ventricular impairment. The main challenges are to differentiate these two states and then to determine whether the left ventricle is likely to recover after aortic valve surgery.

Exhaustive echocardiography is necessary including the use of dobutamine stress. The most secure guides to severe aortic stenosis are a mean transaortic pressure difference > 30 mm Hg and effective orifice area < 1.2 cm^2 during dobutamine stress.

However, the presence of left ventricular contractile reserve more closely determines outcome after surgery than do markers of stenosis. Surgery is most clearly indicated if there is severe aortic stenosis and an increase in the systolic velocity integral by >20% during dobutamine infusion.

Low ''gradient'', low flow aortic stenosis: key points

- A low left ventricular ejection fraction with high peak transaortic velocity is an appropriate response to high afterload and does not imply a poor left ventricle
- Low gradient, low flow aortic stenosis is defined by a left ventricular ejection fraction < 40%, mean ''gradient'' < 30 mm Hg and effective orifice area < 1.0 cm^2
- Dobutamine stress echocardiography is necessary
- Severe aortic stenosis is defined by a mean gradient > 30 mm Hg at any time during the dobutamine study provided the effective orifice area stays < 1.2 cm^2
- Contractile reserve is shown by a rise in systolic velocity integral > 20%
- Aortic valve replacement is indicated with severe stenosis and contractile reserve

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- ► **This is the definitive paper on the use of dobutamine stress echocardiography to predict outcome in low gradient, low flow aortic stenosis.**

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